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Oral Oncolytics

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Disclosures

- I have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

Objectives

- Review select oral oncolytic approvals in 2019
- Discuss the challenges associated with oral oncolytics
- Identify possible solutions to challenges associated with oral oncolytics

Background

- Historically, chemotherapy has been administered by intravenous infusion in an oncology inpatient unit, clinic or a physician's office
- First oral oncolytics approved in 1953
  - Mercaptopurine
  - Methotrexate
  - 1953-2014: 29 agents approved in 61 years, **averaging ~2 agents per year**
  - 2019: **7 agents approved in 1 year**
  - It is estimated that **25%-30%** in the research pipeline are oral

Weingart SN et al. 2008;6 Suppl 3:S1-14.

Advantages

- Increased control and convenience
- Potential increase in the quality of life
- Potential reduction in travel costs and use of healthcare resources
- Sustained medication exposure

Disadvantages

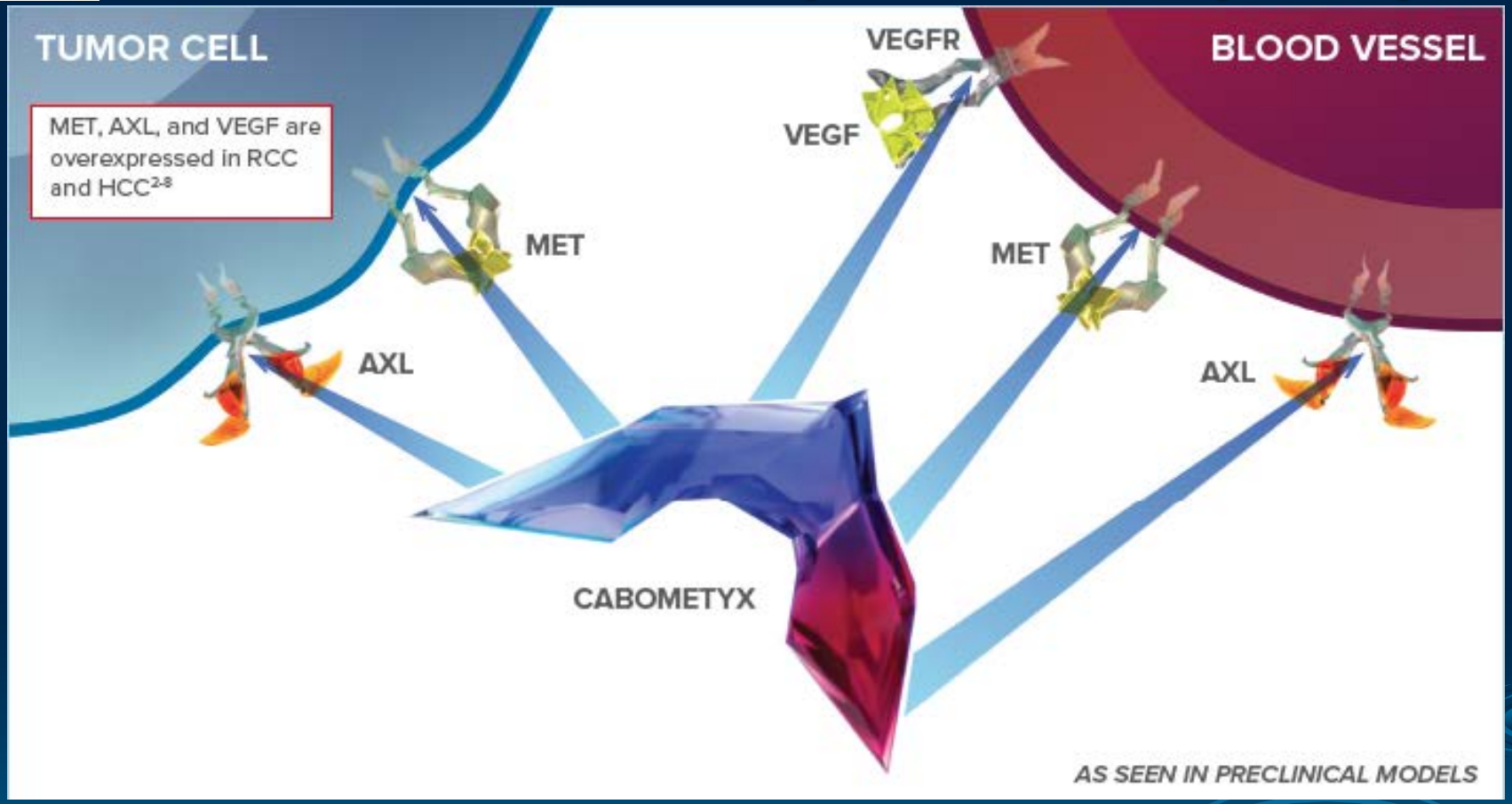
- Lack of coordinated care
- Increased errors
- Nonadherence
- Limited and difficulty monitoring

Weingart SN et al. 2008;6 Suppl 3:S1-14.

Oral Oncolytic Approvals in 2019

- Cabozantinib: Hepatocellular carcinoma, January 14, 2019
- Trifluridine-tipiracil: Gastric or gastroesophageal junction (GEJ) adenocarcinoma, February 22, 2019
- **Alpelisib: Breast cancer, May 24, 2019**
- **Erdafitinib: Urothelial carcinoma, April 12, 2019**
- **Darolutamide: Prostate cancer, July 30, 2019**
- Apalutamide: Prostate cancer, September 17, 2019
- Lenvatinib: Endometrial carcinoma, September 17, 2019
- Niraparib: Ovarian, fallopian tube, or primary peritoneal cancer, October 23, 2019
- Enzalutamide: Prostate cancer, December 16, 2019

Cabozantinib (Cabometyx®)



- Indication: Patients with hepatocellular carcinoma after prior therapy with sorafenib

Cabozantinib [package insert]. Alameda, CA: Elexisis; 2019

Cabozantinib (Cabometyx®)

Dose	Strengths	Drug-Drug Interactions	Adverse Effects
• 60 mg po daily without food	• 60 mg • 40 mg • 20 mg	• Strong CYP3A4 inhibitors: If can't avoid, reduce cabozantinib dose Strong CYP3A4 inducers: If can't avoid, increase cabozantinib dose	• Hemorrhage • Perforations and fistulas • Thrombotic events • Hypertension and hypertensive crisis • Diarrhea • Palmar-plantar erythrodysesthesia (PPE) • Proteinuria • Osteonecrosis of the jaw • Wound complications • Reversible posterior leukoencephalopathy syndrome

Cabozantinib [package insert]. Alameda, CA: Elexisis; 2019

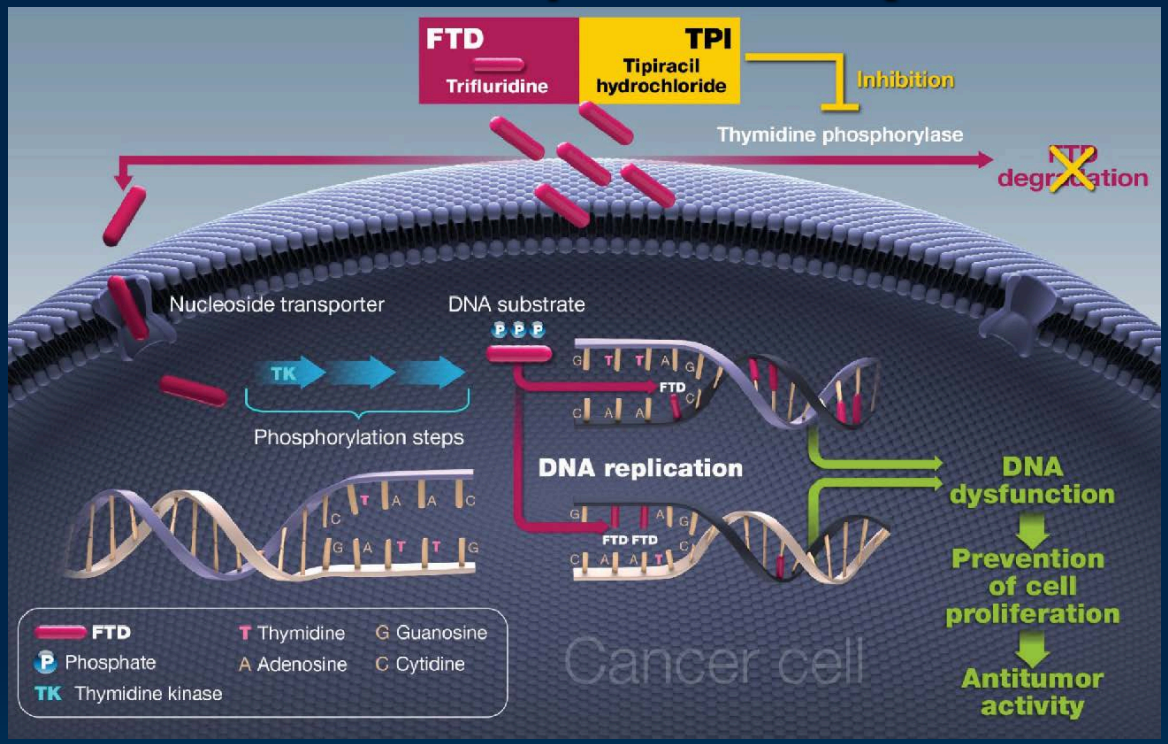
Cabozantinib (Cabometyx®)

Pearls

- Cabometyx tablets ≠ cabozantinib capsules
- Do not give with food
  - ≥1 hour before or ≥2 hours after eating
- Take missed dose if <12 hours to next dose
- Hold ≥28 days prior to surgery
- Diarrhea (any grade: 63%, Grade 3: 11%):
  - Intolerable Grade 2, Grade 3, or Grade 4: Hold until Grade 1; resume at ↓ dose
- PPE (any grade: 44%, grade 3: 13%):
  - Intolerable Grade 2 or Grade 3: Hold until Grade 1; resume at ↓ dose
  - Prophylaxis: Moisturizing creams containing keratolytics
  - Treatment: Urea, clobetasol, pain control
- Hypertension and hypertensive crisis (any grade: 36%, Grade 3:17%):
  - Uncontrolled hypertension: Hold; resume at ↓ dose once controlled
  - Severe hypertension not medically manageable or hypertensive crisis: Discontinue

Cabozantinib [package insert]. Alameda, CA: Elexisis; 2019

Trifluridine-Tipiracil (Lonsurf®)



- Indication: Patients with metastatic gastric or GEJ adenocarcinoma previously treated with ≥2 prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy

Trifluridine-Tipiracil [package insert]. Princeton, NJ: Taiho; 2019

Trifluridine-Tipiracil (Lonsurf®)

Dose	Strengths	Drug-Drug Interactions	Adverse Effects

• 35 mg/m^2/dose orally twice daily with food on
  • Days 1-5
  • Days 8-12
  • Every 28 days
• Dosing based on trifluridine
• Round nearest 5 mg
• Maximum: 80 mg
	• 15 mg trifluridine/ 6.14 mg tipiracil
	• 20 mg trifluridine/ 8.19 mg tipiracil
		• None in in vitro studies	• Severe myelosuppression (neutropenia, anemia, thrombocytopenia, and febrile neutropenia)
			• Gastrointestinal toxicity

Trifluridine-Tipiracil [package insert]. Princeton, NJ: Taiho; 2019

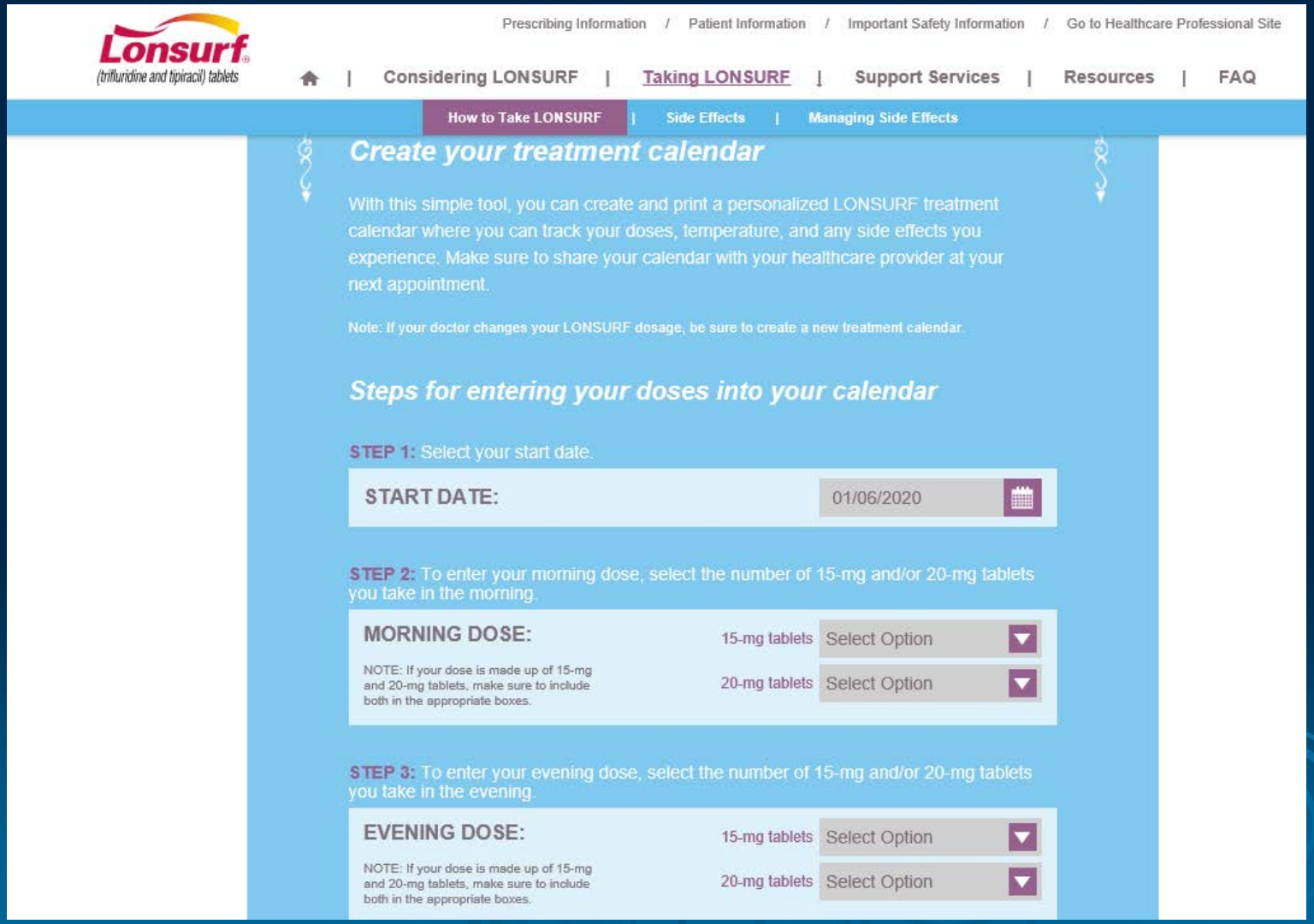
Trifluridine-Tipiracil (Lonsurf®)

Pearls

- If stored outside of original bottle, discard after 30 days
- Dosing schedule:
  - Monday to Friday
  - 2 weeks on, 2 weeks off
- Complete blood cell (CBC) prior to and on Day 15 each cycle
- Hold for any of the following:
  - Absolute neutrophil count (ANC) <500/mm^3 or febrile neutropenia
  - Platelets <50,000/mm^3
  - Grade 3 or 4 non-hematologic adverse effects
  - Recover then ↓ dose by 5 mg/m^2/dose
- Maximum of 3 dose reductions
- Do not ↑ dose after reduction
- 20 mg/m2 po BID not tolerable: Permanently discontinue

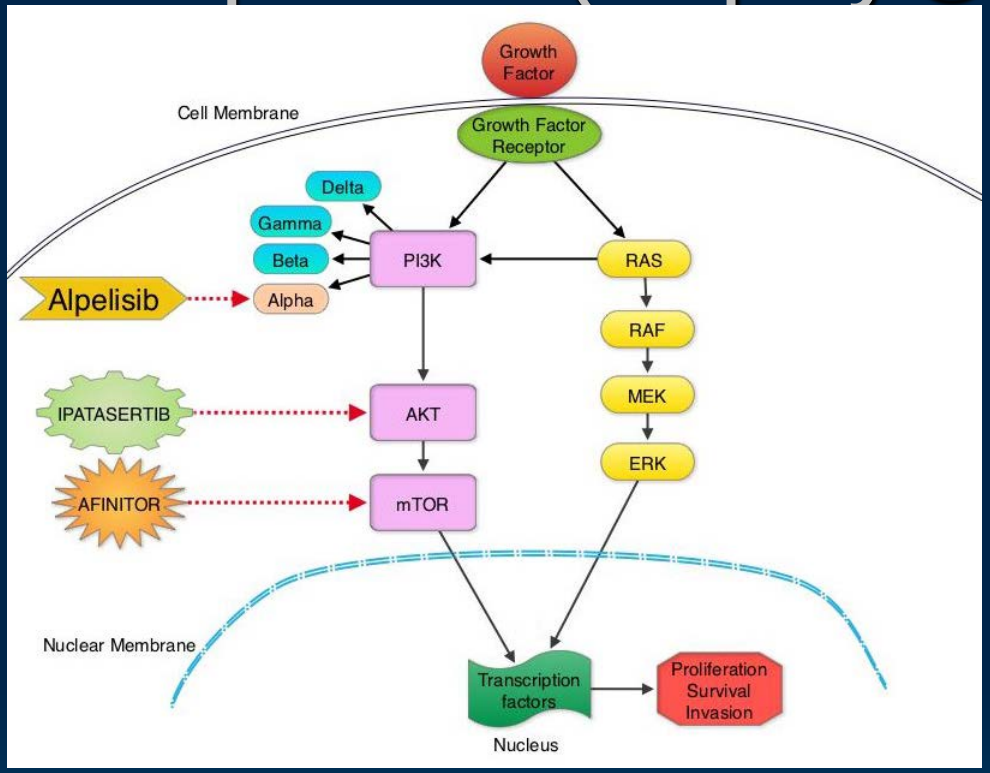
Trifluridine-Tipiracil [package insert]. Princeton, NJ: Taiho; 2019

Trifluridine-Tipiracil (Lonsurf®)



Tips & Tools. LONSURF® (trifluridine and tipiracil) tablets. https://www.lonsurf.com/patient-resources/tools.

Alpelisib (Piqray®)



- In combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer

Alpelisib [package insert]. East Hanover, NJ: Novartis; 2019

Alpelisib (Piqray®)

Dose	Strengths	Drug-Drug Interactions	Adverse Effects
• 300 mg (two 150 mg film-coated tablets) po daily with food	• 50 mg • 150 mg	• CYP3A4 inducer: Avoid • BCRP inhibitors: Avoid, if unable to use alternative drugs, closely monitor for increased adverse reactions • CYP2C9 substrates: Closely monitor	• Severe hypersensitivity • Severe cutaneous reactions • Hyperglycemia • Pneumonitis • Diarrhea

Alpelisib [package insert]. East Hanover, NJ: Novartis; 2019

Alpelisib (Piqray®)

Dose Level	Dose[1]	Number and Strength of Tablets
Starting dose	300 mg once daily	Two 150 mg tablets
First-dose reduction	250 mg once daily	One 200 mg tablet and one 50 mg tablet
Second-dose reduction	200 mg once daily	One 200 mg tablet

[1]Only one dose reduction is permitted for pancreatitis
[2]If further dose reduction below 200 mg once daily is required

Severity of Diarrhea	Recommendations
Grade 1 (increase of <4 stools per day over baseline)	• Initiate medical therapy and monitor
Grade 2 (increase of 4-6 stools per day over baseline)	• Initiate or intensify medical therapy and monitor • Hold until Grade ≤1: Resume at same dose level
Grade 3 (increase of ≥7 stools per day over baseline) and Grade 4 (life-threatening consequences)	• Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt dose until recovery to Grade ≤1, then resume at the next lower dose level

Alpelisib [package insert]. East Hanover, NJ: Novartis; 2019

Alpelisib (Piqray®)

Severity of Hyperglycemia	Recommendations
Grade 1 (FPG >ULN-160 mg/dL)	• Initiate or intensify anti-diabetic treatment • SOLAR-1 trial: • Metformin 500 mg po daily → 500 mg po twice daily → 500 mg po with breakfast and 1000 mg po with dinner → 1000 mg po twice daily
Grade 2 (FPG >160-250 mg/dL)	• Follow Grade 1 recommendations

Grade 3 (>250-500 mg/dL)	• Follow Grade 1 recommendations and consider additional anti-diabetic medications X1-2 days until improvement
	• FPG ↓ to ≤160 mg/dL within 3 to 5 days: Resume at 1 lower dose level
	  • Not within 3-5 days: Consult physician
	  • Not within 21 days: Permanently discontinue

Grade 4 (>500 mg/dL) 17	• Follow Grade 1 recommendations, re-check FPG within 24 hours and as clinically indicated • FPG ↓ to ≤500 mg/dL: Follow Grade 3 recommendations • FPG >500 mg/dL: Permanently discontinue

Alpelisib [package insert]. East Hanover, NJ: Novartis; 2019

Alpelisib (Piqray®)

Severity of Rash	Recommendations
Grade 1 (<10% body surface area (BSA) with active skin toxicity)	• Topical corticosteroid treatment • Consider + oral antihistamine
Grade 2 (10-30% BSA with active skin toxicity)	• Initiate or intensify topical corticosteroid + oral antihistamine • Consider + low dose systemic corticosteroid
Grade 3 (e.g., severe rash not responsive to medical management) (>30% BSA with active skin toxicity)	• Initiate or intensify topical/systemic corticosteroid + oral antihistamine treatment • Once ≤Grade 1: • 1st occurrence: Resume at the same dose level 2nd occurrence: Resume at next lower dose level
Grade 4 (e.g., severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue

Alpelisib [package insert]. East Hanover, NJ: Novartis; 2019

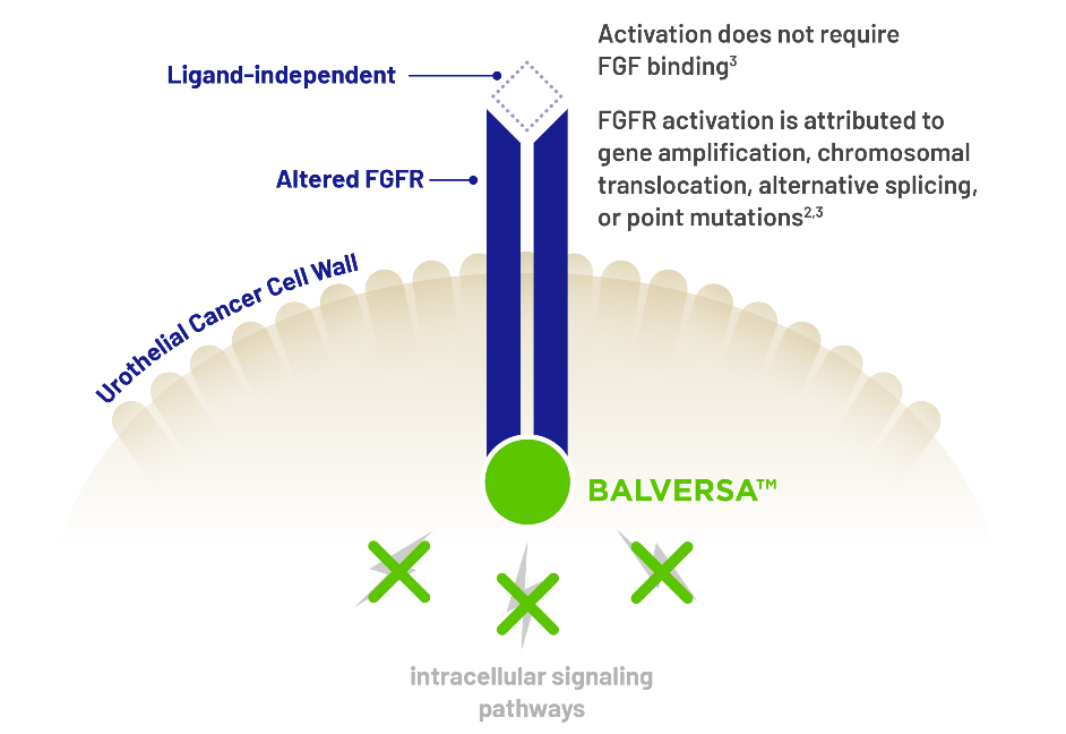
Alpelisib (Piqray®)

Pearls

- Take with food
- Missed dose: Take up to 9 hours after usual time
- Hyperglycemia (any grade: 6%, Grade 3: 33%)
  - Monitor blood glucose and/or FPG
    - First 2 weeks: At least weekly
    - Thereafter: At least 1X every 4 weeks, and as clinically indicated
    - Hyperglycemia occurs: As clinically indicated, and ≥ 2X weekly until normal
    - During anti-diabetic therapy: At least weekly X 8 weeks → biweekly and as clinically indicated
    - Monitor HbA1c every 3 months and as clinically indicated
- Diarrhea: (any grade: 58%, Grade 3: 7%)
- Pneumonitis: Signs and symptoms

Alpelisib [package insert]. East Hanover, NJ: Novartis; 2019

Erdafitinib (Balversa®)



- Patients with locally advanced or metastatic urothelial carcinoma with susceptible fibroblast growth factor receptor 3 (FGFR3) or FGFR2 genetic alterations, when the disease has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy

Erdafitinib [package insert]. Northbrook, IL: Astellas; 2019

Erdafitinib (Balversa®)

Dose	Strengths	Drug-Drug Interactions	Adverse Effects
• 8 mg (two 4 mg tablets) po daily • ↑to 9 mg (three 3 mg tablets) po daily based on serum phosphate (PO_4) levels and tolerability at 14-21 days	• 3 mg • 4 mg • 5 mg	Avoid, if not possible, monitor adverse reactions and consider dose modifications: • Strong CYP2C9 or CYP3A4 inhibitors and inducers • Moderate CYP2C9 or CYP3A4 inducers • Serum phosphate level-altering agents • CYP3A4 substrates • OCT2 substrates • P-gp substrates	• Hyperphosphatemia • Ocular disorders

Erdafitinib [package insert]. Northbrook, IL: Astellas; 2019

Erdafitinib (Balversa®)

Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Dose Reduction	5th Dose Reduction
9 mg → (three 3 mg tablets)	8 mg (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop
8 mg → (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop	

Phosphate Levels	Dose Adjustment	Recommendations
5.6-6.9 mg/dL	None	• Continue
7.0-9.0 mg/dL	Hold	• Hold until ↓ <5.5 mg/dL (or baseline) • Restart at same dose level • Hyperphosphatemia lasting >1 week: Consider dose reduction
>9.0 mg/dL	Hold	• Hold until ↓ <5.5 mg/dL (or baseline) • Restart at 1 dose level lower
>10.0 mg/dL or significant alteration in baseline renal function or Grade 3 hypercalcemia	Hold	• Hold until ↓ <5.5 mg/dL (or baseline) • Restart 2 dose levels lower

Erdafitinib [package insert]. Northbrook, IL: Astellas; 2019

Erdafitinib (Balversa®)

Grade of Central Serous Retinopathy/Retinal Pigment Epithelial Detachment (CSR/RPED)	Recommendations

Grade 1: Asymptomatic; clinical or diagnostic observations only	• Hold until resolution
	  • Within 4 weeks: Resume at 1 lower dose level
	  • Then, if no recurrence X 1 month: Consider re-escalation
	• Not resolved but stable X2 consecutive eye exams: Resume at 1 lower dose level

Grade 2: Visual acuity 20/40 or better or ≤3 lines of decreased vision from baseline	• Hold until resolution • Resolves within 4 weeks: May resume at the next lower dose level
Grade 3: Visual acuity worse than 20/40 or >3 lines of decreased vision from baseline	• Hold until resolution • Within 4 weeks: Resume 2 dose levels lower • Recurs: Consider permanent discontinuation
Grade 4: Visual acuity 20/200 or worse in affected eye	• Permanently discontinue

Erdafitinib [package insert]. Northbrook, IL: Astellas; 2019

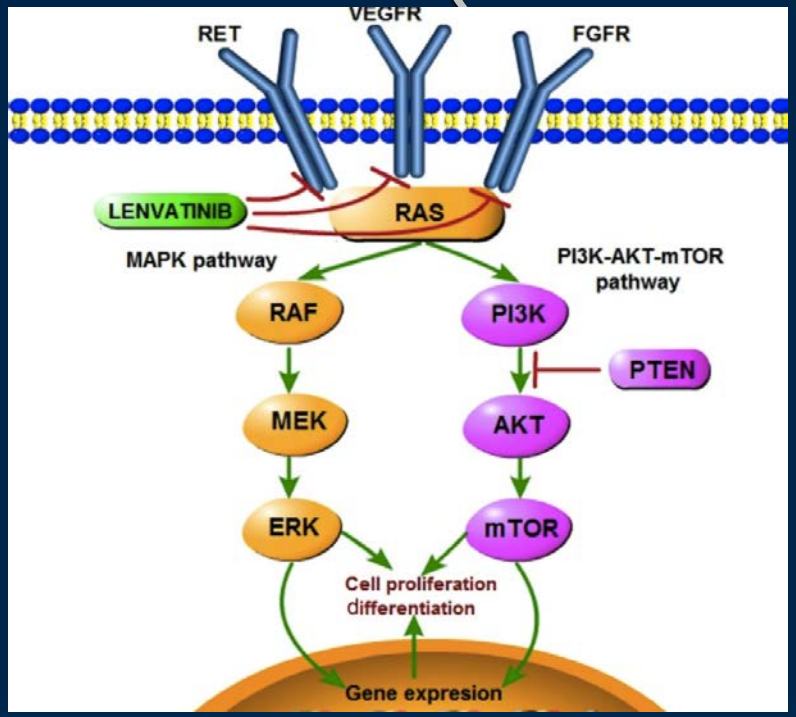
Erdafitinib (Balversa®)

Pearls

- Missed dose: Take as soon as possible. No double doses
- Hyperphosphatemia (any grade: 76%):
  - Levels 14-21 days after initiation
  - Monitor levels monthly
  - Restrict phosphate intake to 600-800 mg daily
  - >7.0 mg/dL: Consider adding oral phosphate binder until ↓ <5.5 mg/dL
- Ocular disorders (any grade: 25%, Grade 3: 3%)
  - All patients should receive ocular demulcents as needed
  - Eye exams
    - During first 4 months: Monthly
    - Thereafter: Every 3 months

Erdafitinib [package insert]. Northbrook, IL: Astellas; 2019

Lenvatinib (Lenvima®)



- In combination with pembrolizumab, for patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation

Lenvatinib [package insert]. Woodcliff Lake, NJ: Eisai; 2019

Lenvatinib (Lenvima®)

Dose	Strengths	Drug-Drug Interactions	Adverse Effects
• 20 mg po daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks	• 4 mg • 10 mg	• Drugs that prolong the QT interval: Avoid	• Hypertension • Proteinuria • Diarrhea • QT interval prolongation • Hypocalcemia • Impairment of thyroid stimulating hormone suppression/thyroid dysfunction • Wound healing complication

Lenvatinib [package insert]. Woodcliff Lake, NJ: Eisai; 2019

Lenvatinib (Lenvima®)

Adverse Reaction	Severity	Recommendations
Hypertension	Grade 3	• Persists despite optimal antihypertensive therapy: Hold • ≤Grade 2: Resume at reduced dose
	Grade 4	• Permanently discontinue
Cardiac Dysfunction	Grade 3	• Hold until ↓to Grade 0 to 1 or baseline • Depending on severity/persistence: Resume at a reduced dose or discontinue
	Grade 4	• Permanently discontinue
Arterial thromboembolic event	Any	• Permanently discontinue
Hepatotoxicity	Grade 3 or 4	• Hold until ↓to Grade 0 to 1 or baseline • Depending on severity and persistence: Either resume at a reduced dose or discontinue • Hepatic failure: Permanently discontinue
Renal failure or impairment	Grade 3 or 4	• Hold until ↓to Grade 0 to 1 or baseline • Depending on severity and persistence: Resume at a reduced dose or discontinue

Lenvatinib [package insert]. Woodcliff Lake, NJ: Eisai; 2019

Lenvatinib (Lenvima®)

Adverse Reaction	Severity	Recommendations
Proteinuria	≥2 g proteinuria in 24 hours	• Hold until ≤2 g/24 hours • Resume at a reduced dose • Nephrotic syndrome: Permanent discontinue
Gastrointestinal perforation	Any	• Permanently discontinue
Fistula formation	Grade 3 or 4	• Permanently discontinue
QT prolongation	>500 ms or >60 ms ↑from baseline	• Hold until ≤480 ms or baseline • Resume at a reduced dose
Reversible Posterior Leukoencephalopathy Syndrome	Any	• Hold until resolved • Depending on severity and persistence: Resume at a reduced dose or discontinue
Other	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Hold until ↓to Grade 0 to 1 or baseline • Resume at reduced dose
	Grade 4 adverse reaction	• Permanently discontinue

Lenvatinib [package insert]. Woodcliff Lake, NJ: Eisai; 2019

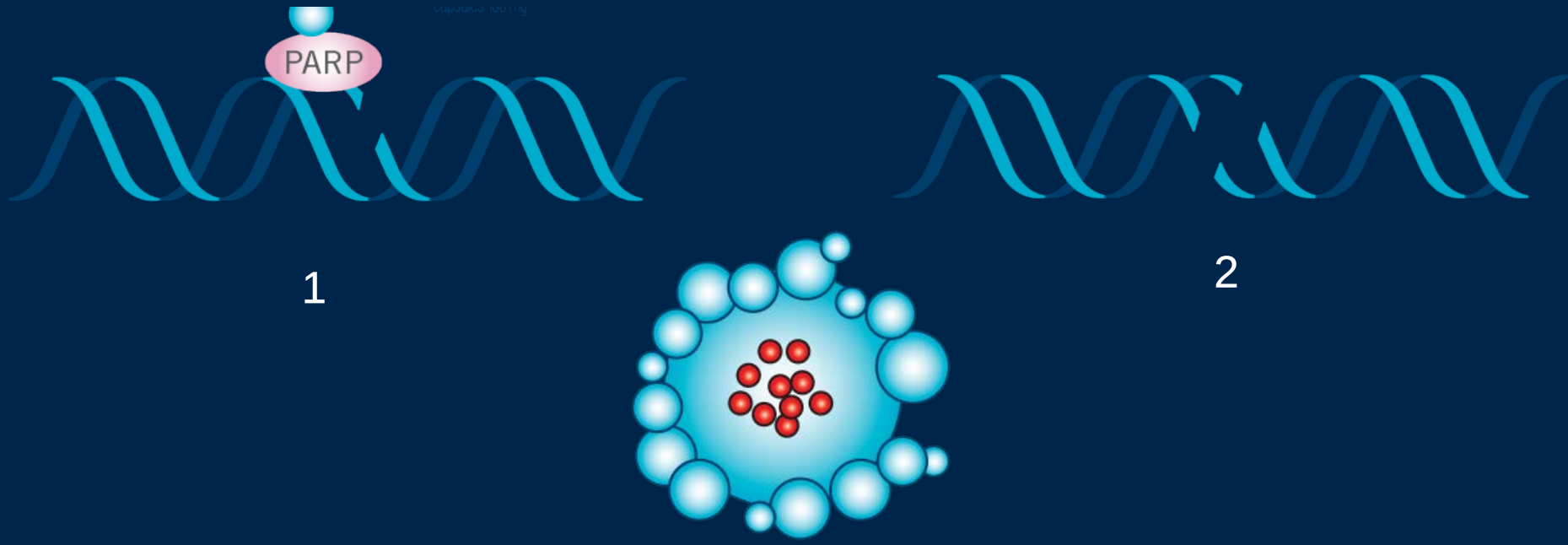
Lenvatinib (Lenvima®)

Pearls

- Missed dose: Next dose is due within 12 hours, skip the missed dose
- If cannot swallow capsules, can take with medicine cup and liquid
- Hypertension: Monitor after 1 week → every 2 weeks X first 2 months, → ≥ monthly
- Proteinuria: Monitor prior to and periodically during treatment.
  - ≥2+: Obtain 24-hour urine protein
- Diarrhea: Take loperamide 4 mg po, then 2 mg every 4 hours or after each loose stool
- QT interval prolongation:
  - Monitor and correct electrolyte abnormalities
  - Monitor electrocardiograms in patients with cardiac conditions or on agents that prolong the QT interval
- Impairment of thyroid stimulating hormone suppression/thyroid dysfunction: Monitor prior to and monthly during treatment
  - Treat hypothyroidism accordingly
- Wound healing complication: Hold for ≥6 days prior to surgery

Lenvatinib [package insert]. Woodcliff Lake, NJ: Eisai; 2019

Niraparib (Zejula®)



- Patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status

Niraparib [package insert]. Waltham, MA: Tesaro; 2019

Niraparib (Zejula®)

Dose	Strengths	Drug-Drug Interactions	Adverse Effects
• 300 mg (three 100 mg capsules) po daily	• 100 mg	• No clinical drug interaction studies have been performed	• Myelodysplastic syndrome/acute myeloid leukemia • Bone marrow suppression • Cardiovascular effects

Niraparib [package insert]. Waltham, MA: Tesaro; 2019

Niraparib (Zejula®)

Dose Modifications for Adverse Reactions	
Dose Level	Dose
Starting dose	300 mg/day (three 100 mg capsules)
First dose reduction	200 mg/day (two 100 mg capsules)
Second dose reduction	100 mg/day* (one 100 mg capsule)

Dose Modifications for Non-Hematologic Adverse Reactions	
Non-hematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	• Hold ≤ 28 days or until resolution • Resume at a reduced dose • ≤2 dose reductions
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	• Discontinue medication

*If further dose reduction below 100 mg/day is required, discontinue

Niraparib [package insert]. Waltham, MA: Tesaro; 2019

Niraparib (Zejula®)

Dose Modifications for Non-Hematologic Adverse Reactions

Platelet count <100,000/µL	First occurrence: • Hold ≤28 days and monitor blood counts weekly until platelet counts ↑≥100,000/µL • Resume at same or reduced dose • If platelet count is <75,000/µL, resume at a reduced dose
	Second occurrence: • Hold ≤28 days and monitor blood counts weekly until platelet counts ↑≥100,000/µL • Resume at a reduced dose • > 28 days of holding not resolved or already reduced to 100 mg po daily: Discontinue
Neutrophil <1,000/µL or Hemoglobin <8 g/dL	• Hold ≤28 days and monitor blood counts weekly until neutrophil counts ↑≥1,500/µL or hemoglobin ↑≥9 g/dL • Resume at a reduced dose • If not acceptable >28 days from dose interruption period or already on 100 mg po daily: Discontinue
Hematologic adverse reaction requiring transfusion	• Platelet count ≤10,000/µL: Consider transfusion • Other risk factors such as co-administration of anticoagulation or antiplatelet drugs: Consider interrupting these drugs and/or transfusion at a higher platelet count • Resume at a reduced dose

*If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue

Niraparib [package insert]. Waltham, MA: Tesaro; 2019

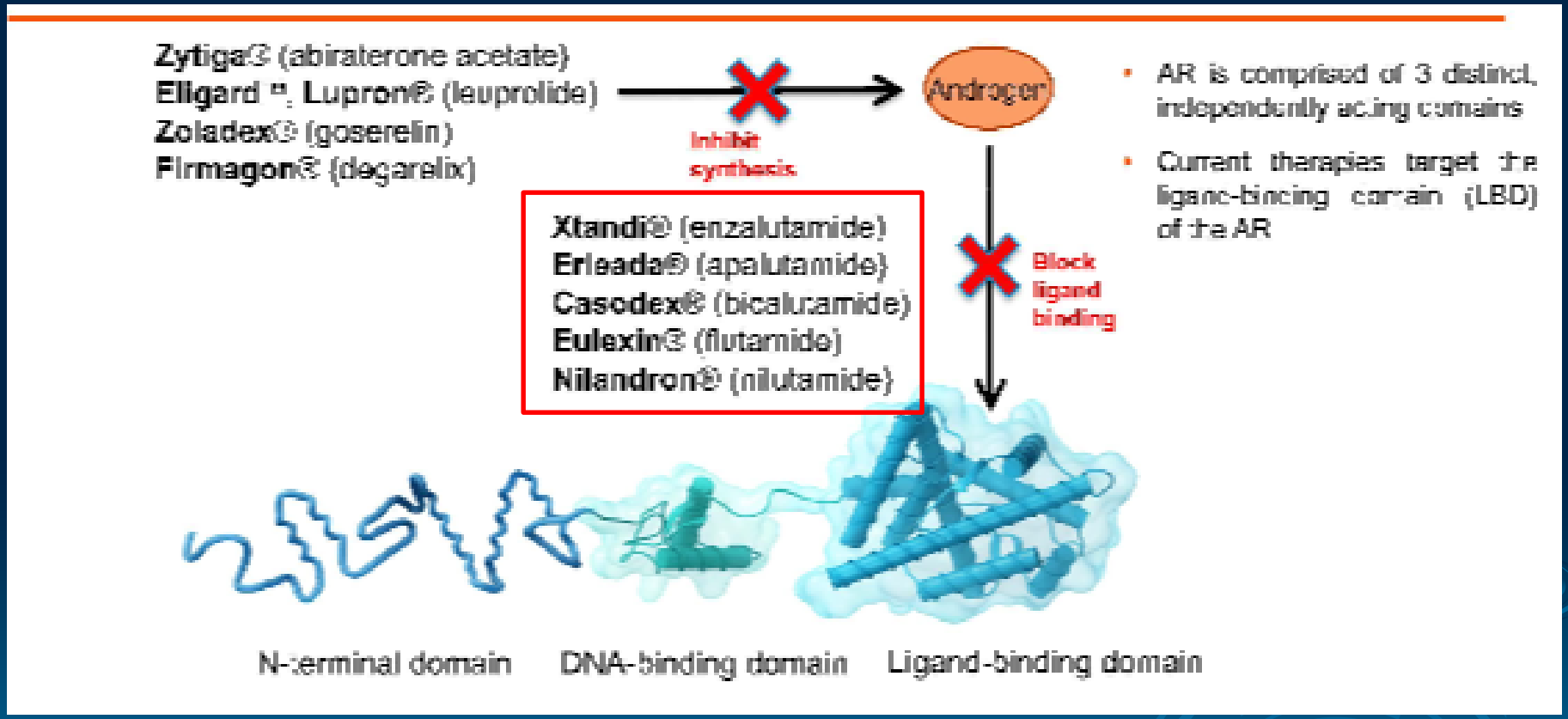
Niraparib (Zejula®)

Pearls

- Nausea: Bedtime administration
- Myelodysplastic syndrome/acute myeloid leukemia: Developed <2 months to >4 years of therapy
- Bone marrow suppression:
  - Do not start until ≤ Grade 1 hematological toxicity
  - Complete blood count
    - First month: Weekly
    - Next 11 months: Monthly and periodically
    - Hematological toxicities do not resolve ≤28 days following interruption: Discontinue and refer to hematologist
- Cardiovascular effects: Monitor blood pressure and heart rate
  - First 2 months: At least weekly
  - First year: Monthly and periodically

Niraparib [package insert]. Waltham, MA: Tesaro; 2019

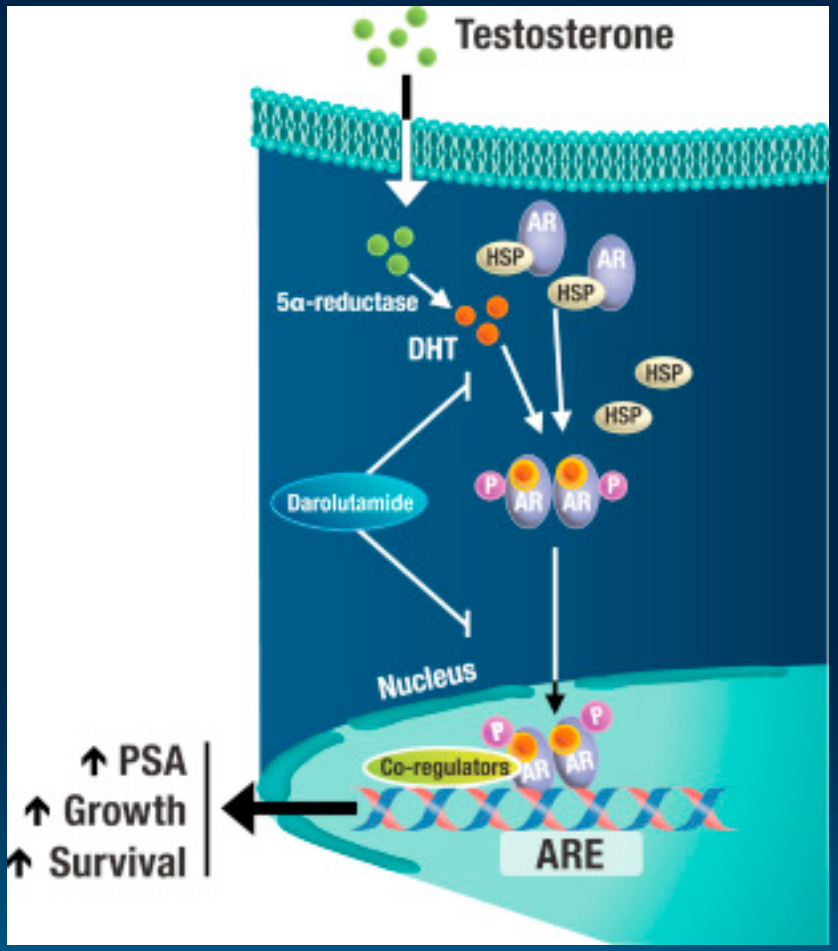
Androgen Receptor Inhibitors: Enzalutamide (Xtandi®) and Apalutamide (Erleada®)



- Patients with metastatic castration-sensitive prostate cancer

Darolutamide [package insert]. Whippany, NJ: Bayer; 2019
Apalutamide [package insert]. Guarbo, PR: Janssen Ortho LLC; 2019
Enzalutamide [package insert]. Northbrook, IL: Astellas; 2019

Darolutamide (Nubeqa®)



- Patients with non-metastatic castration-resistant prostate cancer

Darolutamide [package insert]. Whippany, NJ: Bayer; 2019

Androgen Receptor Inhibitors

	Dose	Strengths	Drug-Drug Interactions
Darolutamide	600 mg (two 300 mg tablets) po twice daily	• 300 mg	• Combined P-gp and strong or moderate CYP3A4 inducers: Avoid • Combined P-gp and strong CYP3A4 inhibitors: Monitor more frequently for adverse reactions • BCRP substrates: Avoid, if not, monitor for adverse reactions and consider ↓ BCRP substrate drug dose
Apalutamide	240 mg (four 60 mg tablets) po daily	• 60 mg	• Concomitant use with sensitive substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1: Avoid
Enzalutamide	160 mg (four 40 mg capsules) po daily	• 40 mg	• CYP2C8 inhibitors and CYP3A4 inducers: Avoid, if not, ↓to 80 mg po daily • CYP3A4 inducers: Avoid, if not possible, ↑ to 240 mg po daily

Darolutamide [package insert]. Whippany, NJ: Bayer; 2019
Apalutamide [package insert]. Guarbo, PR: Janssen Ortho LLC; 2019
Enzalutamide [package insert]. Northbrook, IL: Astellas; 2019

Androgen Receptor Inhibitors

	Adverse Effects	Pearls

Darolutamide	• Fatigue
	• Pain in extremity
	• Rash
	• Neutropenia
	• AST ↑
	• Bilirubin ↑
		• Missed dose: Take as soon as you remember. Do not double up.
		• Should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy
		• Darolutamide:
		  • Take with food
		  • Twice daily
		  • ≥Grade 3 toxicity or an intolerable: Hold or ↓ to 300 mg po twice daily until symptoms improve → may restart at 600 mg po twice daily
		• Apalutamide and enzalutamide:
		  • Seizure: Permanently discontinue
		  • Ischemic cardiovascular events: Optimize management of cardiovascular risk factors
		  • Fractures: Refer to guidelines for use of bone-targeted agents
		• Enzalutamide
		  • PRES: Seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, ± associated hypertension

Apalutamide	• Ischemic cardiovascular events • Fractures • Falls • Seizure	
Enzalutamide	• Seizure • Posterior Reversible Encephalopathy Syndrome (PRES) • Hypersensitivity • Ischemic heart disease	

Darolutamide [package insert]. Whippany, NJ: Bayer; 2019
Apalutamide [package insert]. Guarbo, PR: Janssen Ortho LLC; 2019
Enzalutamide [package insert]. Northbrook, IL: Astellas; 2019

Oral Oncolytic Challenges

- There is a need to properly manage and monitor patients who are self-administering their treatments at home
- Presents challenges to health care providers and patients
  - Common misconceptions and safety issues regarding oral oncolytics
  - Financial toxicity
  - Maximizing the efficacy of oral oncolytics
- Oncology pharmacists are uniquely positioned to mitigate these challenges

Weingart SN et al. 2008;6 Suppl 3:S1-14.

Handling

- Easily administered, however, have exposure risks, similar to intravenous formulations
- General misconception: Exposure risk is low and therefore oral oncolytics present little risk and are safer to handle
- Accidental exposure to oral oncolytics can occur at various stages during handling
  - Storage
  - Handling
  - Administration
  - Disposal
- Guidelines around safe handling are still evolving

Goodin S et al. *J Oncol Pract*. 2011;7(1):7–12. doi:10.1200/jop.2010.000068

Handling Recommendations for Health Care Providers

- Storage:
  - Store in a designated area separate from noncytotoxic agents
- Handling:
  - Use personal protective clothing and equipment to minimize exposure and health risks
  - Separate equipment should be used for cytotoxic and noncytotoxic agents
  - Manipulations should be performed in a biological safety cabinet
  - Should not be dispensed using automatic counting machines

Goodin S et al. *J Oncol Pract*. 2011;7(1):7–12. doi:10.1200/jop.2010.000068

Handling Recommendations for Health Care Providers

- Disposal and Cleaning of Contaminated Materials:
  - All disposable protective clothing and disposable: Cytotoxic waste
  - All nondisposable materials: Wash or decontaminate thoroughly after use
- Training and Competencies for Safe Handling:
  - Orientation programs and routine training courses with competencies on managing exposures and handling
  - A primary educator within a health care institution should be established as a source of referral and continued education on oral oncolytics

Goodin S et al. *J Oncol Pract*. 2011;7(1):7–12. doi:10.1200/jop.2010.000068

Handling Recommendations for Patients and their Caregivers

Do's

- Store according to package insert
- Keep in original container
- Use gloves and wash hands thoroughly before and after glove application
- Pour the oral chemotherapy agent into a bowl, or the lid of the pill bottle, and then pour the pills into the patient's hand or mouth
- Soiled items should be kept and washed separately from other laundry

Don'ts

- Leave medication in open areas, near sources of water, direct sunlight
- Store medications in the areas where food or drinks are stored or consumed
- Crush, break, or chew tablets
- Discard medication down the toilet or in the garbage

Goodin S et al. *J Oncol Pract*. 2011;7(1):7–12. doi:10.1200/jop.2010.000068

Financial Toxicity

- The advent of new options have improved patient outcomes
  - Accompanied with an increase in the monetary burden of cancer treatment
- Cancer has become the second most expensive disease in the United States
- Annual estimated cost estimated to increase from 124 billion dollars in 2010 to 157 billion dollars in 2020
- Drug prices are a function of several factors
  - The cost of research and development
  - Manufacturing costs
  - Market pressures

Tran G, Zafar SY. *Ann Transl Med*. 2018;6(9):166. doi:10.21037/atm.2018.03.28

Financial Toxicity

- Public and private payers have implemented cost sharing measures that shift more of the financial burden to patients
- Patients have been subjected to higher
  - Deductibles
  - Co-insurance
  - Copayments
  - Out-of-pocket (OOP) expenses
- Patients with cancer have OOP expenses that are estimated to be 976 to 1,170 dollars higher than patients without cancer

Tran G, Zafar SY. *Ann Transl Med*. 2018;6(9):166. doi:10.21037/atm.2018.03.28

Financial Toxicity

- Financial toxicity: Negative impact of a cancer diagnosis on a patient's financial well-being resulting from direct or indirect costs
  - Objective financial burden
    - OOP expenses
    - Indirect costs
  - Subjective financial distress
    - Material conditions that arise from increased direct and indirect costs
    - The psychological response as a result of efforts necessary to cope with the increased costs
    - The coping behavior itself that patients adopt to manage their medical care while experiencing increased expenses

Tran G, Zafar SY. *Ann Transl Med*. 2018;6(9):166. doi:10.21037/atm.2018.03.28

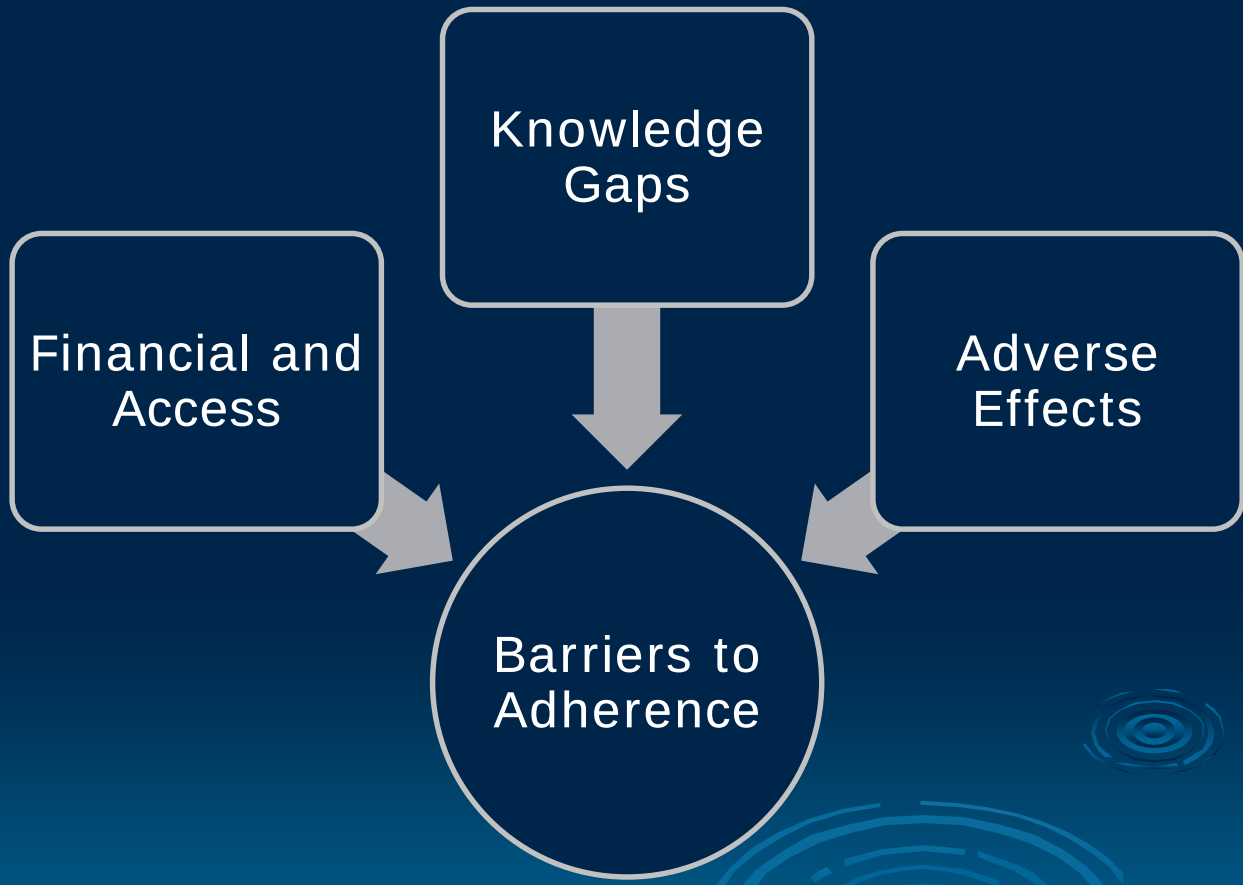
Financial Toxicity

- Yabroff et al: 20.4% of adult cancer survivors reported experiencing financial difficulties
  - Being unable to pay for their cancer-related medical bills
  - Having to borrow money
  - Going into debt
  - Filing for bankruptcy
- To cope with financial toxicity, patients often resort to medication nonadherence

Tran G, Zafar SY. *Ann Transl Med*. 2018;6(9):166. doi:10.21037/atm.2018.03.28

Adherence

- Variability in adherence: 50-100%
- Both over- and under-adherence can result in negative outcomes
  - Higher mortality
  - Increased toxicity
  - Delays and changes in treatment
  - Higher health utilization and total cost of care



Weingart SN et al. 2008;6 Suppl 3:S1-14.

Barriers to Adherence: Financial and Access

- Access barriers can be related to financial barriers
- Examples:
  - Prior authorizations
  - High formulary tier
  - Quantity limits or not covered at all
  - Delays in receiving prescription
- Solutions:
  - Dedicated medication assistance team
  - External financial assistance programs

Weingart SN et al. 2008;6 Suppl 3:S1-14.

Barriers to Adherence: Financial and Access

- Resources
  - Manufacturer's Patient Assistance Program
  - ACC Patient Assistance & Reimbursement Guide: https://www.accc-cancer.org/home/learn/publications/patient-assistance-and-reimbursement-guide
  - NCCN Virtual Reimbursement Resource Room: https://www.nccn.org/reimbursement_resource_room/default.aspx
  - CancerCare: www.cancercare.org
  - Cancer Family Relief Fund: www.cancerfamilyrelieffund.org
  - Cancer Finances: www.cancerfinances.org
  - Cancer Financial Assistance Coalition: www.cancerfac.org
  - Leukemia & Lymphoma Society: www.lls.org/support/financial-support
  - Medicine Assistance Tool: www.medicineassistancetool.org
  - NeedyMeds: www.needymeds.org

Barriers to Adherence: Knowledge Gaps

- Health literacy
- May lack knowledge about
  - Administration schedules
  - Adverse effect management
- Patient education program
  - Include family members or caregivers when possible
  - Patient-centered
  - Teach-back method
  - Provide information in multiple formats
  - Multiple times

Weingart SN et al. 2008;6 Suppl 3:S1-14.

Barriers to Adherence: Knowledge Gaps

28-day dosing schedule

Start Date: **1/11/2020**

Morning Dose: **1 x 15-mg tablets* 1 x 20-mg tablets***
Evening Dose: **1 x 15-mg tablets* 1 x 20-mg tablets***

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1/11 _ AM _ PM Temp: Side Effects: I feel:
1/12 _ AM _ PM Temp: Side Effects: I feel:	1/13 _ AM _ PM Temp: Side Effects: I feel:	1/14 _ AM _ PM Temp: Side Effects: I feel:	1/15 _ AM _ PM Temp: Side Effects: I feel:	1/16 Rest Temp: Side Effects: I feel:	1/17 Rest Temp: Side Effects: I feel:	1/18 _ AM _ PM Temp: Side Effects: I feel:
1/19 _ AM _ PM Temp: Side Effects: I feel:	1/20 _ AM _ PM Temp: Side Effects: I feel:	1/21 _ AM _ PM Temp: Side Effects: I feel:	1/22 _ AM _ PM Temp: Side Effects: I feel:	1/23 Rest Temp: Side Effects: I feel:	1/24 Rest Temp: Side Effects: I feel:	1/25 Rest Temp: Side Effects: I feel:
1/26 Rest Temp: Side Effects: I feel:	1/27 Rest Temp: Side Effects: I feel:	1/28 Rest Temp: Side Effects: I feel:	1/29 Rest Temp: Side Effects: I feel:	1/30 Rest Temp: Side Effects: I feel:	1/31 Rest Temp: Side Effects: I feel:	2/1 Rest Temp: Side Effects: I feel:
2/2 Rest Temp: Side Effects: I feel:	2/3 Rest Temp: Side Effects: I feel:	2/4 Rest Temp: Side Effects: I feel:	2/5 Rest Temp: Side Effects: I feel:	2/6 Rest Temp: Side Effects: I feel:	2/7 Rest Temp: Side Effects: I feel:	

Questions for my healthcare provider:

*Tablet strength of LONSURF is based on 1 active part of the medicine.

Tips & Tools. LONSURF® (trifluridine and tipiracil) tablets. https://www.lonsurf.com/patient-resources/tools.

Barriers to Adherence: Cognitive and Knowledge Gaps

- Solutions continued:
  - Multinational Association for Supportive Care in Cancer (MASCC) Oral Agent Teaching Tool (MOATT): https://www.mascc.org/assets/Guidelines-Tools/moatt_v1.2.pdf
  - Dana-Farber oral chemotherapy fact sheet: https://www.dana-farber.org/health-library/articles/oral-chemotherapy-fact-sheet/
  - Counseling sheets: www.oralchemoedsheets.com, www.chemocare.com

ORAL CHEMOTHERAPY EDUCATION

ACCC Association of Community Cancer Centers | HOPA Hematology/Oncology Pharmacy Association | NCODA National Community Oncology Dispensing Association, Inc. PASSION FOR PATIENTS | ONS Oncology Nursing Society

DAROLUTAMIDE

Name of your medication

Generic name — Darolutamide
Brand name — Nubeqa® (NOO-be-kə)

Approved uses

Darolutamide is used to treat men with prostate cancer.

Dose and schedule

Taking darolutamide as instructed is important to allow your treatment to be as effective as possible, so here are some key points to remember.

- ☐ Your dose may vary, but the usual dose of darolutamide is 600 milligrams (600 mg) to be taken by mouth at a scheduled time twice a day.
- ☐ Darolutamide should be taken with food, at the same times each day.
- ☐ Darolutamide should be taken whole and not crushed, cut, or dissolved. If you are unable to swallow darolutamide, talk to your care provider or pharmacist for possible options.
- ☐ If you miss or vomit a dose of darolutamide, follow these guidelines:
  - Take it as soon as you remember, unless your next scheduled dose is due within 6 hours. Take the next dose at your regular time.
  - Do not take 2 doses at one time.
  - Be sure to write down if you miss a dose, and let your care provider know about any missed doses.

Drug and food interactions

- ☐ Darolutamide has many drug interactions. Please inform your care providers of all prescription medications, over-the-counter medications, vitamins, and herbal products.
- ☐ Grapefruit or grapefruit juice may interact with darolutamide; avoid eating or drinking this during treatment with darolutamide.
- ☐ Talk with your care provider or pharmacist before taking new medications or supplements, or receiving any vaccines.

Storage and handling

Handle darolutamide with care. Just like when chemotherapy is given into the vein, this drug can be toxic, and exposure of the drug to others should be limited.

- ☐ Store darolutamide at room temperature (68°F–77°F) in a dry location away from light.
- ☐ Keep darolutamide out of reach of children and pets.
- ☐ Leave darolutamide in the provided packaging until it is ready to be taken.

Darolutamide. OralChemoEdSheets. https://www.oralchemoedsheets.com/index.php/sheet-library/24-available/generic/357-darolutamide

ORAL CHEMOTHERAPY EDUCATION

DAROLUTAMIDE

Possible Side Effect	Management
Decreased white blood cells (WBCs) and increased risk for infection	Your WBCs should be monitored by a simple blood test. When your WBCs are low, you are at a greater risk of having an infection. Take the following precautions to protect yourself from infection. • Wash your hands often, especially before eating and after using the bathroom. • Avoid crowds and people with fevers, flu, or other infection. • Bathe regularly to keep good personal hygiene. Contact your care provider if you experience any signs or symptoms of an infection: • Fever (temperature more than 100.4°F or 38°C) • Chills • Sore throat • Burning with urination • Unusual tiredness • A sore that becomes red, is draining, or does not heal Check with your care provider before taking any medicine for a fever or chills.

Serious side effects

If you experience ANY uncontrolled side effect, call your physician or healthcare center immediately:

_____ (INSTITUTIONAL CONTACT INFO)

Handling body fluids and waste

Since darolutamide remains in your body for several days after it is taken, some of the drug may be present in urine, stool, sweat, or vomit. Once you have started to take darolutamide, it is important to adhere to the following instructions every day for as long as your treatment lasts. This is to keep yourself, loved ones, and the environment as safe as possible.

- ☐ Pregnant women should avoid touching anything that may be soiled with body fluids from the patient.
- ☐ Toilet and septic systems
  - You may use the same toilet, septic tank, and/or sewer that you usually use. If you have a low-flow toilet, close the lid and flush twice to ensure that all waste has been discarded.
  - If the toilet or toilet seat becomes soiled with urine, stool, or vomit, clean the surfaces before other people use the toilet.
  - Wash hands with soap and water after using the toilet.
- ☐ If you need a bedpan, be sure your caregiver knows to wear gloves to assist with cleanup and to wash the bedpan with soap and water every day.
- ☐ If you do not have good control of bladder or bowels, use a disposable pad with a plastic back, a diaper, or a sheet to absorb body waste.
- ☐ Wash any skin that has been exposed to body waste or darolutamide with soap and water.

Darolutamide. OralChemoEdSheets. https://www.oralchemoedsheets.com/index.php/sheet-library/24-available/generic/357-darolutamide

ORAL CHEMOTHERAPY EDUCATION

DAROLUTAMIDE

- Linens or clothing that are soiled with body fluids or body waste should be washed separately from other linens and clothing. If you do not have a washer, place the soiled linens in a plastic bag until they can be washed.
- Wash hands with soap and water after touching linens or clothing that may be soiled with body fluids.

Pregnancy, sexual activity, and contraception

- Women should not become pregnant and men should not get a partner pregnant while taking darolutamide. Males and females of childbearing age and potential should use effective contraception during therapy and for a minimum of 1 week after the last dose of darolutamide.
- Effective contraception could include 1 or more of the following: oral contraceptive, barrier methods, etc.
- It is safe to hug and kiss. Special precautions may be needed for sexual activity while on oral chemotherapy, and you are encouraged to ask your care team for assistance.
- Darolutamide can cause serious birth defects and loss of pregnancy. Do not take darolutamide if you are pregnant or think you might be pregnant.

Obtaining medication

- Talk with your care provider about the process for obtaining your darolutamide.

_____ (PHARMACY OR SPECIALTY PHARMACY CONTACT INFO)

Additional resources

Product website: https://www.nubeqa-us.com
Product prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212099Orig1s000lbl.pdf

Updated – November 9, 2019

Additional instructions

_____
_____
_____
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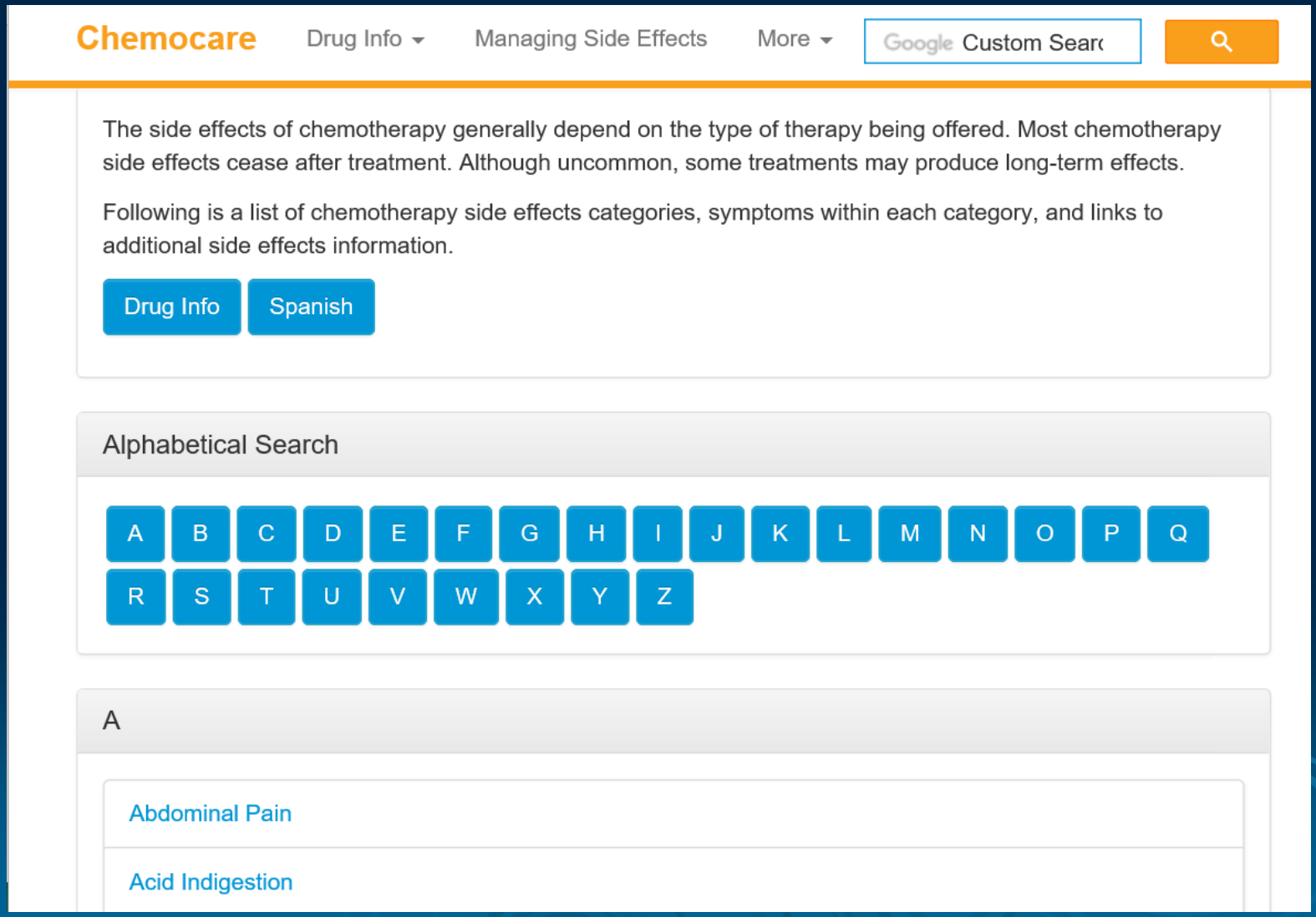
Darolutamide. OralChemoEdSheets. https://www.oralchemoedsheets.com/index.php/sheet-library/24-available/generic/357-darolutamide

Barriers to Adherence: Adverse Effects

- Misconception: Adverse effects from oral oncolytics will be less severe than side effects from intravenous therapy
- May adjust their adherence to minimize adverse effects
- Solutions:
  - Ensure patients, families, and caregivers understand
    - Possible adverse effects
    - How to manage adverse effects
    - When and whom to call before stopping or altering drug administration
    - Address fears regarding reporting adverse effects
  - Managing side effects: http://chemocare.com/chemotherapy/side-effects/default.aspx

Weingart SN et al. 2008;6 Suppl 3:S1-14.

Barriers to Adherence: Adverse Effects



Managing Side Effects. Chemocare. http://chemocare.com/chemotherapy/side-effects/default.aspx.

Summary

- First oral oncolytics approved in 1953
  - Mercaptopurine, methotrexate
- Proper precautions should still be taken when handling
- Adverse effects are still possible
- Increase in oral oncolytics
  - 2019: 7 agents approved in 1 year
- Advantages: Decreased trips to physician's office or clinic
- Disadvantages: Financial toxicity, minimal monitoring and maximizing efficacy largely dependent upon patient
- Solutions: Patient assistance programs/external programs, education/counseling, calendars and other tools for maximizing adherence

Weingart SN et al. 2008;6 Suppl 3:S1-14.
Tran G, Zafar SY. *Ann Transl Med*. 2018;6(9):166. doi:10.21037/atm.2018.03.28
Goodin S et al. *J Oncol Pract*. 2011;7(1):7–12. doi:10.1200/jop.2010.000068

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Questions